Mechanism of Syncope and Action of Drugs in Complete Heart Block

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SUMMARY

The syncopal attacks of complete heart block may be due either to ventricular standstill or to ventricular acceleration including fibrillation. As treatment may be harmful unless the underlying mechanism in each case is determined, it is important to apply the available methods for differentiation.

Epinephrine and certain related compounds (sympathomimetic amines) are the only effective substances in the therapy of ventricular arrest.

Isopropyl nor-epinephrine is a most potent drug in the prevention and treatment of ventricular arrest and has the advantage that it does not dispose to fibrillation.

Quinidine is unreliable and probably hazardous in the control of ventricular fibrillation in heart block as it appears to precipitate this arrhythmia.

Preliminary observations indicate that ectopic ventricular rhythms are also induced by procaine amide in complete heart block.

Isuprel® may be of value in the therapy of ventricular acceleration, by preventing the ventricular arrest which frequently follows the initial acceleration.

THE chief therapeutic problem in complete heart block is the prevention of syncopal attacks. The syndrome of syncope with slow pulse was described in 1827 by Robert Adams[1] of Dublin; the patient, whose pulse rate was 30 per minute, had dyspnea, cough and attacks of fainting. In the same year William Burnett[2] reported a similar case and called attention to the fact that Morgagni had described two patients with epilepsy and slow pulse in 1761. However, general attention was not attracted to this condition until William Stokes[23] published four cases in 1846. Since that time, syncopal attacks associated with heart block have been known as the Adams-Stokes syndrome. For many years, it was generally accepted that the mechanism underlying the Adams-Stokes syndrome was asystole of the ventricles. The cardiac arrest might occur (a) during the transition from normal rhythm to complete block or (b) in the midst of complete block. The Adams-Stokes seizures have been defined as attacks which "occur in patients with auriculoventricular block, when the ventricular diastole is sufficiently prolonged to result in a severe grade of cerebral ischemia."[17]

In 1941 Parkinson, Papp and Evans,[18] in an excellent analysis of 64 cases in which electrocardiograms were made during syncopal attacks of heart block, emphasized that ventricular asystole was not the only mechanism. Of the 64 patients, 18 had ventricular tachycardia and fibrillation followed by ventricular standstill, 13 had ventricular tachycardia and fibrillation without standstill and 33 had ventricular standstill alone. These observers defined the Adams-Stokes attack as "that condition which is seen in patients with complete heart block who suffer from recurrent attacks of loss of consciousness due to ventricular standstill, ventricular tachycardia, ventricular fibrillation or a combination of these." Although the report of Parkinson and his associates emphasized the frequency of ventricular acceleration as the basis of the Adams-Stokes attack, earlier observers[3, 4, 5, 6, 8, 9] had reported this mechanism in heart block. Schwartz and co-workers[19, 20, 21] in 1932 and in a series of later papers carried out a most detailed analysis of graphic records before, during, and after a seizure.

It is apparent that rational therapy directed at the prevention of the Adams-Stokes attack necessitates a recognition of the underlying cardiac mechanism. An electrocardiogram taken during a seizure will (Figures 1 and 3a) demonstrate the mechanism clearly. Since it is not always possible to obtain a record during an attack, other methods may be required and certain observations will lead to suspicion of ventricular acceleration or fibrillation. In ventricular asystole, the transition from the basic rhythm to the cessation of cardiac activity is usually abrupt (Figure 1). However, when the mechanism is ventricular fibrillation, it has been observed by Schwartz and co-workers[19, 20, 21] that, preceding the seizures, there is consistently a regular or irregular acceleration of the heart. Recently Schwartz and co-workers[21] stated that "transient ventricular fibrillation in man has never been observed to be ushered in abruptly without such premonitory signs." These premonitory disturbances of rhythm may be suspected in several ways. First, the patient himself may be aware of an increase in heart rate preceding a syncopal attack. Second, when attacks

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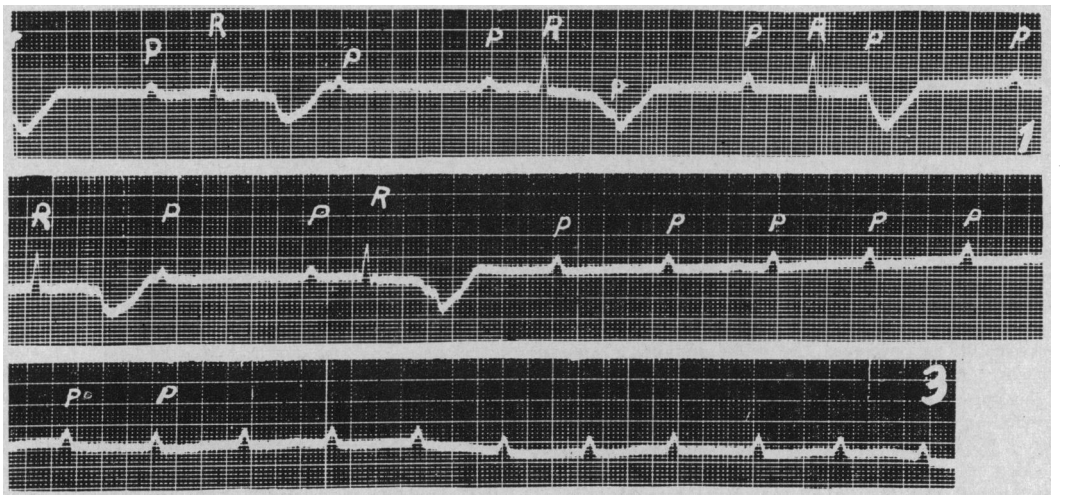

Figure 1.—Upper strip shows complete heart block, ventricular rate 23 beats per minute. Second strip shows the onset of ventricular standstill. After the first two ventricular complexes, the record shows only auricular waves. The lower strip is a continuation of the record.

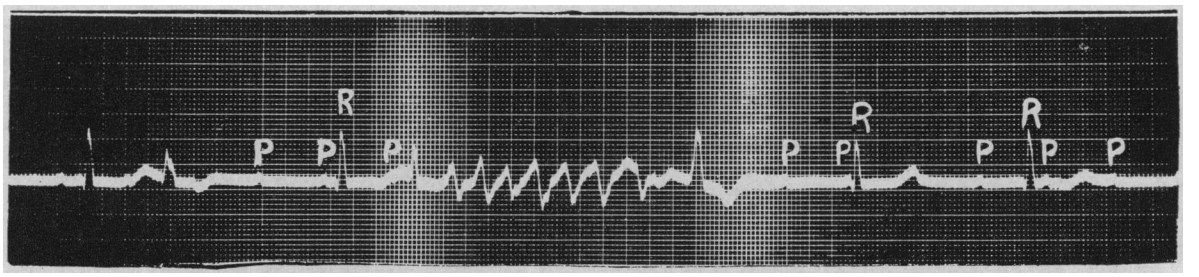

Figure 2.—Complete heart block, showing the basic rhythm interrupted by a series of ventricular oscillations.

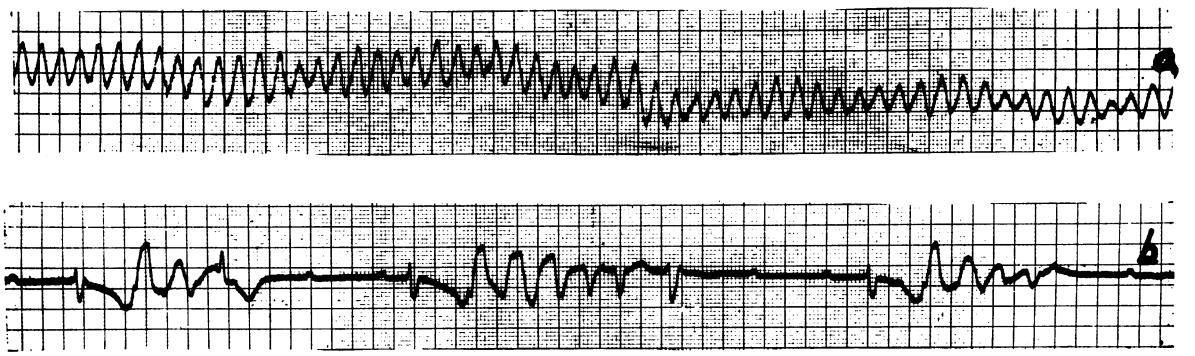

Figure 3.—Strip *A*, taken during a syncopal attack, shows ventricular fibrillation. Strip *B*, taken between attacks, shows complete heart block and the basic pattern alternating with short runs of aberrant ventricular oscillations.

are frequent, an observant nurse may note acceleration before the pulse disappears completely and syncope occurs. Third, a physician, on auscultation of the heart between attacks, may hear frequent interruptions of the slow basic rhythm by short runs of rapid and weak beats, most of which cannot be felt at the wrist. The audibility of these contractions becomes progressively weaker after the basic ventricular beat. During these arrhythmic periods, pallor of the face may be noted and the patient may complain of a weak or sinking sensation. Fourth, it is frequently possible in a routine electrocardiogram, especially if long strips are taken, to observe the basic pattern interrupted by recurrent runs of ventricular oscillations (Figures 2 and 3b). A fifth point which strongly suggests ventricular acceleration and fibrillation as the mechanism is the ineffectiveness of epinephrine and related compounds, which actually may prolong and increase the frequency of attacks.

Certain of these features are illustrated in the case of a patient with heart block observed in 1933. Ventricular fibrillation was suspected although an electrocardiogram was not obtained during an attack.

CASE REPORT

The patient was a 76-year-old obese, dyspneic woman who complained of fainting spells. Syncopal attacks started on December 22. She had two attacks on that day and on the following. On December 23 an attack observed by a physician consisted of jerking of the extremities and a short period of unconsciousness during which the pulse was absent. Upon examination, the blood pressure was noted to be 230 mm. of mercury systolic and 60 mm. diastolic. The pulse was irregular and the rate 40 beats per minute. Some pulmonary congestion was present. An electrocardiogram indicated complete heart block. During the examination, the patient suddenly gasped for breath, the eyes became fixed and she became unconscious. The pulse and heart sounds were absent. After the attack, when the patient was conscious, the pulse rate was 48 and there were coupled beats. Periodically, on auscultation of the heart, this rhythm was interrupted by a series of rapid, weak beats, which could not be palpated at the wrist. The patient continued to have three or four attacks, lasting up to four or five minutes, a day. Barium chloride given orally had no influence on the attacks, and they persisted after the subcutaneous administration of epinephrine although the pulse rate rose to 56 per minute. Upon inspection of the routine electrocardiogram, occasional series of aberrant ventricular oscillations (Figure 2) were noted. A diagnosis of complete heart block with syncope due to ventricular fibrillation was made. Quinidine sulfate was given orally in doses of 300 mg. three times a day. The patient continued to have from one to three attacks of syncope a day. The pulse rate was usually 40, but immediately after one mild attack an irregular pulse with a rate of 54 beats a minute was noted. On the seventh day of hospitalization the patient died after prolonged syncope.

In that case several features suggested ventricular fibrillation as the mechanism of the syncopal attacks. On auscultation of the heart, the normal rhythm was periodically interrupted by a series of rapid, weak beats which could not be palpated at the wrist. A relatively rapid irregular rate was noted immediately after one of the seizures—a phenomenon described by Schwartz and co-workers.[19, 20, 21] There was a continuance of the attacks after the administration of epinephrine despite a definite increase in the ventricular rate. The presence of irregular aberrant ventricular oscillations in the electrocardiogram could be considered as almost conclusive evidence that longer periods of this rhythm were present during the syncopal seizures.

In the following case, the attacks were so frequent that it was possible to make many records during the seizures. In all of them ventricular fibrillation was noted. Even without those tracings, however, the diagnosis would have been strongly suspected because of the presence of short runs of ventricular oscillations in the electrocardiograms made between the attacks.

CASE REPORT

The patient, a 78-year-old woman, entered the hospital with a history of repeated syncopal attacks for one month. The blood pressure was 220 mm. of mercury systolic and 70 mm. diastolic. The heart was moderately enlarged and the pulse rate was 40 per minute. In an electrocardiogram, complete heart block was noted. During a period of five days the patient had approximately 200 syncopal attacks, varying from 15 seconds to several minutes in duration. Electrocardiograms made during the attacks showed ventricular fibrillation (Figure 3a). In parts of many tracings made between seizures, complete heart block with a basic ventricular pacemaker from a single focus, was noted. In many portions, this pattern was interrupted by short runs of aberrant ventricular oscillations (Figure 3b).

TABLE 1.—*Effect of Pressure on the Carotid Sinus on the Auricular and the Ventricular Rate in Complete Heart Block*

		After Pressure on the Carotid Sinus	
Auricular Rate	Ventricular Rate	Auricular Rate	Ventricular Rate
80	38	32	38
88	30	45	30
118	25	84	25
100	34	76	34
64	33	33	33
65	29	44	29

As was mentioned previously, ventricular activity of the kind noted in this case may be considered a prefibrillation mechanism and it indicates that ventricular fibrillation is the basis for the syncope.

INFLUENCE OF THE VAGUS NERVE IN COMPLETE HEART BLOCK

Increased activity of the vagus nerve has been considered a possible basis for the critical slowing of the ventricular rate or for the asystole of heart block. If this were the case, the administration of atropine could prevent the inhibition of the ventricles. However, this drug has not been found to be effective in the prevention of syncopal attacks. This is probably due to the fact that there is little or no vagal innervation to the ventricular pacemaker. The absence of a vagal effect on the ventricular pacemaker is indicated by the observation in which carotid sinus pressure was applied in six patients with complete heart block. The effect of this reflex vagus stimulation was observed on the auricular and ventricular rates. There was a reduction of 50 per cent or more in the auricular rate in each patient while the ventricular rate was unaffected (Table 1).

ACTION OF DRUGS THAT STIMULATE THE RHYTHMIC FUNCTION OF THE VENTRICLES

The observations of Danelopolu and Danulescu (1915) on the beneficial action of epinephrine in heart block have been confirmed in many subsequent reports. However, favorable effects have been ascribed from time to time to other unrelated compounds such as nikethamide (Coramine®), Metrazol,® desiccated thyroid and barium chloride. The ventricular standstill in heart block is due to a temporary failure of ventricular automaticity so that no pacemaker is functioning. The effectiveness of a drug in the therapy and prevention of ventricular standstill depends on its ability to increase the rhythmicity or pacemaking property of the ventricles. In previous studies[14, 15] it was concluded that epinephrine and related compounds, sympathomimetic amines, are the only substances which stimulate

this property of the heart. Of a group of these substances studied, epinephrine was the most active in the prevention of cardiac standstill. Two other compounds, ephedrine and Paredrine,® were of interest because they are effective on oral administration. The oral route is desirable in patients with complete heart block with infrequent syncopal attacks, where self-medication for the prevention of attacks is indicated. Paredrine was found to be more active than ephedrine. In six patients with heart block, 100 to 150 mg. of ephedrine sulfate was required to increase the ventricular rate. A similar increase in rate was obtained by giving 60 to 80 mg. of paredrine hydrobromide.

Recently a new epinephrine-like compound, isopropyl nor-epinephrine (Isuprel®) was introduced for the treatment of bronchial asthma.[10] This drug differs chemically from epinephrine in that an isopropyl group on the terminal nitrogen of the side-chain replaces the methyl group of epinephrine. The chief difference in its action is that the pressor effect of other sympathomimetic drugs is either absent or minimal. In a previous study it was noted that Isuprel was very potent in the prevention of cardiac standstill which can be induced in man by pressure on the carotid sinus.[16]

The effect of this drug in heart block was studied by three routes of administration—intravenous, subcutaneous and sublingual.

Intravenous administration. Isuprel 0.02 mg. was injected intravenously in eight patients with heart block and the effects compared with the reactions following the intravenous administration of 0.03 mg. of epinephrine. The procedure was as follows: a control electrocardiogram was made and three blood pressure readings recorded. The drug was then injected and a continuous electrocardiogram made. The blood pressure was recorded 30 seconds after the injection and thereafter at one-minute intervals.

After both drugs, the ventricular rate rose promptly and remained elevated for from seven to fifteen minutes. Following the intravenous dose of 0.03 mg. of epinephrine, the average increase in ventricular rate was 30 beats per minute. The minimum increase was 20 and the maximum 47 beats per minute. Following the injection of 0.02 mg. of Isuprel the average increase in ventricular rate was 22 beats per minute. The range of increase was from 10 to 39 beats per minute. Considering the smaller dose of Isuprel used, the response of the ventricular rate was approximately the same following both drugs. Following the administration of epinephrine, there was a sharp and pronounced rise in the systolic pressure. The diastolic pressure increased a little. After the injection of Isuprel, the systolic pressure rose slightly to moderately in two patients and was unchanged or depressed in six patients. The diastolic pressure was depressed in six and unchanged in two patients.

Subcutaneous administration. The response of the ventricular rate to a subcutaneous injection of epinephrine and of Isuprel was studied in three patients with complete heart block. The dose of epinephrine used was 1 mg., and of Isuprel 0.2 mg. A control electrocardiogram was made and the drug injected. Electrocardiograms then were made at five-minute intervals for fifteen minutes and thereafter every fifteen minutes for from one to two hours. The ventricular rate was increased by both drugs. In each instance the rise in rate following Isuprel was greater than that after epinephrine was given.

Sublingual administration. Following sublingual application of Isuprel in the treatment of bronchial asthma, the patient is frequently conscious of an increase in heart rate, which indicates that there is sufficient absorption of the drug to influence the sinus rate. The drug was administered by this route in four patients with heart block, and electrocardiograms then were made at five-minute intervals for from one to two hours. The dose for each patient was 15 mg. on one trial and 30 mg. on another occasion. The response to both doses was a sustained rise in ventricular rate. The increase in rate varied considerably and was from 3 to 47 beats per minute. The onset of the effect varied from fifteen to thirty minutes after the application of the drug and the duration was from 45 minutes to two hours.

ACTION OF DRUGS ON VENTRICULAR ACCELERATION AND FIBRILLATION

It would seem that the drugs indicated for the prevention and treatment of ventricular acceleration and fibrillation would be the cardiac depressant or antifibrillatory drugs. Quinidine has been used for this purpose in heart block and the reports are conflicting. De Boer[3] reported that quinidine was ineffective in the prevention of ectopic ventricular rhythms in heart block, and that the drug actually induced these rhythms, including ventricular fibrillation. His explanation was that quinidine produced variations in the refractory period irregularly in different parts of the heart, permitting the development of a circulatory wave from reentrant beats. Kerr and Bender[9] described a case of complete heart block in which attacks of ventricular fibrillation occurred during the course of quinidine therapy. Dock,[5] however, concluded that maintenance doses of quinidine prevented attacks of paroxysmal ventricular fibrillation. Escamilla,[6] after prolonged observation of a patient with attacks of paroxysmal ventricular fibrillation, concluded that quinidine seemed to be of some value but that the effect was not sufficiently constant to permit any absolute conclusions as to its efficacy. Schwartz and Jezer[22] made a careful study of two patients with complete heart block who were subject to transient seizures of ventricular fibrillation. Quinine hydrochloride and quinidine were administered intravenously in graded doses. Both drugs, quinine (maximum dose: 0.10 gm.) and quinidine (maximum dose 0.02 gm.) consistently induced either a prefibrillatory mechanism or transient periods of ventricular fibrillation. It is to be noted that the patient in Case 1, reported herein, died in syncope while receiving quinidine therapy. These observations indicate that the administration of quinidine may be hazardous in patients

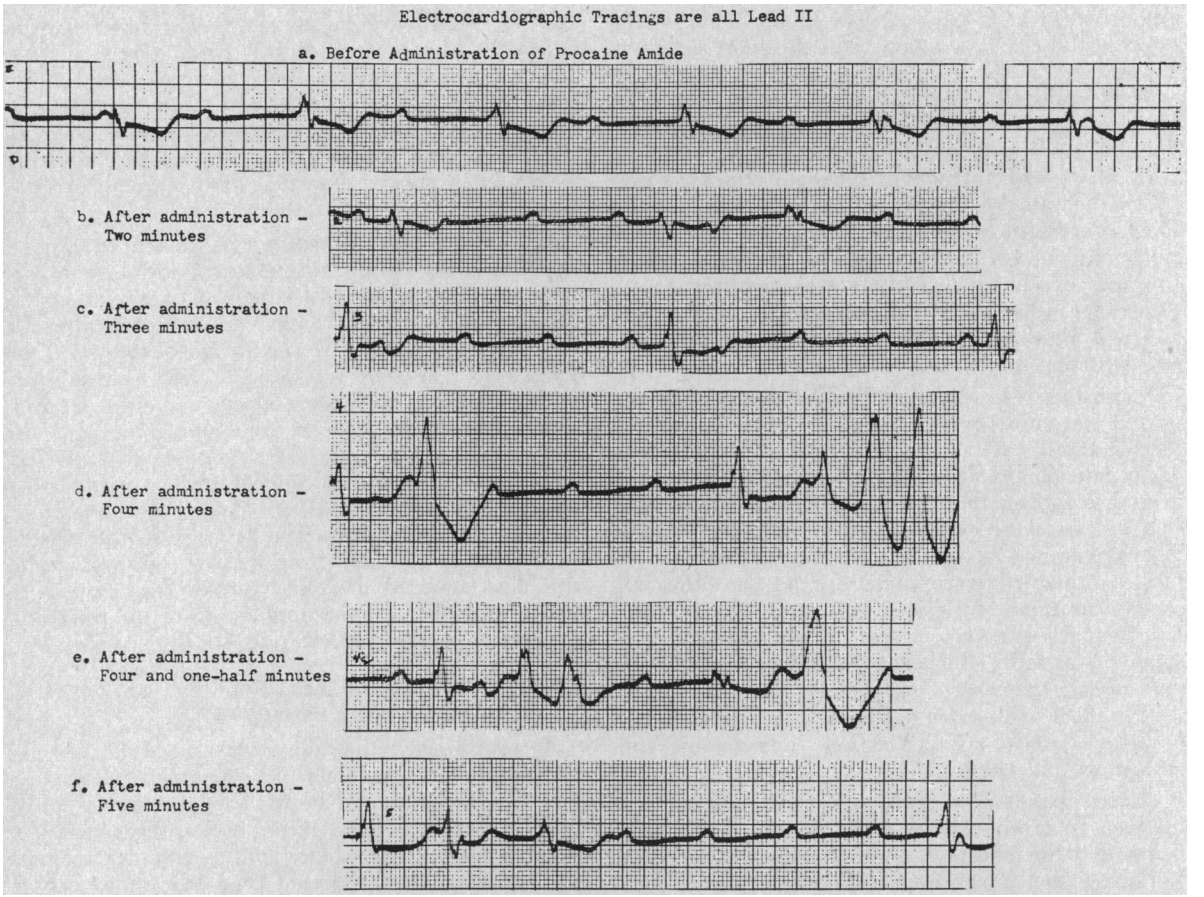

Figure 4.—Strip *A* shows complete heart block, ventricular rate, 34 per minute. Strips *B* and *C*, taken 2 and 3 minutes after the start of an intravenous injection of procaine amide, show a reduction of the ventricular rate to 25 and 20 beats per minute. Strips *D*, *E* and *F*, taken 4, 4½ and 5 minutes after the start of the injection, show most of the basic ventricular complexes replaced by multifocal ectopic ventricular beats.

with complete heart block in whom syncopal attacks are due to ventricular fibrillation.

Recently Mark and co-workers[12] reported the suppression of ventricular premature contractions and the termination of attacks of ventricular tachycardia by the administration of procaine amide (Pronestyl®). In a study of a group of 55 patients, Miller, Nathanson and Griffith[13] noted that this drug abolished ectopic ventricular beats and rhythms with great consistency. It seemed of interest to study the action of this drug in complete heart block. The drug was administered intravenously in four patients. The dose was 500 mg. in one patient, 300 mg. in another and 200 mg. in two patients. In each patient, there was a definite reduction in the ventricular rate. In two patients, the injection of procaine amide was followed by the appearance of ectopic ventricular beats from multiple foci occurring in runs, resembling the prefibrillatory mechanism described by Schwartz and Jezer (Figure 4). In the fourth patient, transient ventricular fibrillation followed the intravenous injection of 200 mg. of procaine amide. In the patient described earlier, in whom ventricular fibrillation was demonstrated as the mechanism of the syncopal attacks, procaine amide administered intravenously and orally had no influence on the frequency or duration of the attacks. These observations indicate that procaine amide, like quinidine, is of no value and is probably contraindicated in the therapy of heart block.

DISCUSSION

The importance of recognition of the mechanism causing the syncopal attack in heart block is apparent, since epinephrine and related compounds, indicated in the therapy of ventricular standstill, are contraindicated in ventricular fibrillation, as these drugs can precipitate this serious arrhythmia. The administration of these compounds, when the seizures are due to ventricular fibrillation, may cause transient arrhythmia to become permanent and fatal. The authors have observed that Isuprel is a very potent compound for the prevention and treatment of ventricular standstill. In addition to its potency, this drug possesses a most important advantage over epinephrine in that it does not appear to dispose the ventricles to fibrillation. Garb and Chenoweth[7] consistently produced ventricular fibrillation in cats during hydrocarbon inhalation by the administration of nor-epinephrine and epinephrine. Isuprel did not produce this arrhythmia, in any instance, under the same conditions. The authors' clinical observations tend to confirm the experimen-

tal studies of Garb and Chenoweth. In one case, that of a patient with complete heart block, the administration of epinephrine was followed by multifocal ectopic ventricular beats, and nor-epinephrine induced transient ventricular fibrillation. Isuprel in this patient produced a greater increase in the basic ventricular rate and yet the drug did not stimulate any lower ventricular rhythmic foci. This tendency for Isuprel to limit its action predominantly to the basic ventricular pacemaker has been quite consistent in the authors' studies. In contrast nor-epinephrine had no effect on the normal ventricular pacemaker and frequently induced multifocal ventricular beats, resembling a prefibrillatory mechanism. Epinephrine, while stimulating the basic pacemaker, also frequently excited lower ventricular foci.

The method of administration of Isuprel in the therapy of cardiac standstill depends upon the urgency of the situation. In the presence of syncope due to cardiac arrest, it may be advisable to administer the drug by intracardiac injection. An effective dose by this route is 0.02 mg. If the ventricular rate is at a critically low level, the drug may be injected intravenously in the same dose. These routes of administration are seldom necessary and the usual mode of application of the drug is by subcutaneous injection. A dose of from 0.14 to 0.2 mg. is usually sufficient to increase the rate of the ventricles. When syncopal attacks are infrequent and self-medication over a long period is desirable, Isuprel may be administered by the sublingual route. A dose of 15 mg. three or four times a day appears to be an effective amount.

It is apparent that there is no safe and effective drug for the prevention of paroxysms of ventricular acceleration or fibrillation in heart block. The reports in the literature indicate that quinidine has either no effect or an unfavorable one. As was noted in the present study, intravenous administration of procaine amide induces ectopic ventricular rhythms in heart block. It is of interest that such a response was not observed when this drug was given to patients who had arrhythmia of other kinds. Although the studies were limited, the results suggested that procaine amide may have undesirable effects in heart block. When the mechanism of the syncope is unknown, Isuprel possesses optimum features in its action, in that it will be effective when the mechanism is ventricular standstill and will exert no unfavorable effect when it is ventricular fibrillation. It would appear that Isuprel may be indicated when the mechanism is known to be ventricular acceleration. Parkinson, Papp and Evans[18] noted that, in a large proportion of patients in whom ventricular acceleration and fibrillation developed, the initial mechanism was followed by a ventricular standstill. Isuprel, by preventing the ventricular arrest, could shorten the duration of syncope. Levine and Matton[11] reported a case of Adams-Stokes syndrome in which, after ventricular fibrillation and asystole lasting five minutes, the patient recovered upon injection of epinephrine into the heart.

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